

AMENDMENT AND RESPONSE TO OFFICE ACTION

REMARKS

Rejection Under 35 U.S.C. § 112, first paragraph – written description

Claims 1-3, 5, 6, 9-23, 29, 33, 39, 43-49, 51, 52 and 54-56 were rejected under 35 U.S.C. §112 as failing to comply with the written description requirement. Applicants respectfully traverse this rejection if applied to the amended claims. Claims 2, 4, 7-10, and 54-56 have been cancelled.

The claims have been amended to recite that the conjugate has a size greater than six nm. Although the applicants believe this was fully supported by the specification as filed, the term “about” was deleted solely to facilitate prosecution.

The claims have all been amended to delete the reference to a linker and to insert instead the specific enzyme cleavage sites that are listed in Table 1 in Appendix A. These are known cleavage sites for specific enzymes, as demonstrated by the literature cited in support of Appendix A. This moots any issue of whether or not there is an enzyme that would cleave an unidentified sequence, or which enzyme, or whether or not it is found in the body. All of these cleavage sites are commercially available and/or described in the literature.

Applicants clearly had possession of the named sequences shown and listed in the specification as originally filed and which are now recited in the independent claims.

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Rejection Under 35 U.S.C. § 102

Claims 1-3, 5, 6, 9-13, 17, 21, 29, 33, 39, 43, 47, 51, 52, and 54-55 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/68145 to Copeland *et al.* ("Copeland"). Claims 2, 4, 7-10, and 54-56 have been cancelled. Applicants respectfully traverse this rejection as applied to the amended claims.

Copeland

Copeland describes compositions containing antineoplastic agents conjugated to enzyme cleavable peptides containing the amino acid recognition sequence of a membrane-bound and/or cell secreted peptidase (abstract). The peptide is capped with a capping group (page 5, line 31). Suitable capping groups are discussed beginning at page 42, line 26. Copeland discloses that polyethylene glycols having the formula



Where t is 1 to 10, preferably t is 1, 2, 3, or 4, more preferably where t is 1 or 2 can be used as amino-capping groups (page 43, lines 17-22). Copeland states that unless otherwise specified, "polyethylene glycol", or "PEG" or "Peg" as an amino capping group having the formula shown below (page 43, lines 20-22):



This molecule contains only two monomer units. THIS MOLECULE HAS A MOLECULAR WEIGHT MAXIMUM (ASSUMING T=10) OF 569.

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The specification at least at page 9, lines 13-18 discloses that macromolecules with sizes above 6 nm (MW ~ 50,000 Da) exhibit marked inhibition on renal clearance. It is clear that the PEG end capping units disclosed in Copeland, which contain between 2 and 10 monomer units, have a molecular weight many many times less than the claimed conjugate size range, and are outside the scope of the claimed conjugates. The claims have been amended to clarify that the polymer, and therefore the conjugate, has a molecular weight of 50,000 or higher or a size of greater than 6 nm. In response to the examiner's question about doxorubicin and a small peptide (even assuming the peptide were as long as 100 amino acids, the cut off used by the patent office), the conjugate would still be substantially smaller. The drug molecular weight is 580; a 100 amino acid peptide, even if made entirely of the largest amino acid, tryptophan, having a molecular weight of 204, the total molecular weight would be 580 plus 20,400, or about 21,000, which is substantially less than 50,000..

Synonyms: Adriamycin® hydrochloride, DOX, Hydroxydaunorubicin hydrochloride
CAS Number: 25316-40-9
Empirical Formula (Hill Notation): $C_{27}H_{34}NO_{11} \cdot HCl$
Molecular Weight: 579.98
Beilstein Registry Number: 4229251
EC Number: 246-818-3
MDL number: MFCD00077757
PubChem Substance ID: 24893465 

Copeland also does not disclose the specifically named enzyme cleavage sequences.

Therefore the claims are novel over Copeland.

Rejection Under 35 U.S.C. § 103

Claims 1-3, 5, 6, 9-14, 17, 18, 21, 22, 29, 33, 39, 43, 44, 47, 48, 51, 52, and 54-56 were rejected under 35 U.S.C. § 102(b) as unpatentable over WO 98/56425 to Duncan ("Duncan"), in

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view of Copeland. Applicants believe the Examiner intended to say the claims were rejected under 35 U.S.C. § 103(a), instead of 102(b), and will present arguments accordingly. Applicants respectfully traverse the rejection of the claims under 35 U.S.C. § 103(a) as applied to the amended claims.

(a) Determining the scope and contents of the prior art

Duncan

Duncan describes a product or kit containing two components, i.e., two pharmaceutical compositions that are arranged or otherwise adapted for sequential administration to a human or animal (page 3, line 36 to page 4, line 2). The first component is an enzyme conjugate, e.g., a composition that contains a pharmaceutically acceptable excipient and an enzyme conjugate (page 4, lines 2-5). The enzyme conjugate may consist of an enzyme covalently bound to a polymeric or other carrier, such that the enzyme conjugate retains its enzyme activity (page 4, lines 5-7). The second component is a prodrug, e.g., a composition that contains a pharmaceutically acceptable excipient and a prodrug (page 4, lines 8-10). The prodrug can be conjugated to a polymeric carrier via a peptide linker (page 10, lines 9-10).

Copeland

Copeland is discussed above.

Secondary Considerations of Obviousness

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The combination of Copeland and Duncan does not lead to a polymer-drug conjugate that avoids the problem with renal clearance. None of the prior art discloses the need to provide a means to prevent renal clearance. Indeed neither even recognize that it is a problem.

As analyzed above, even if the prior art were interpreted to yield the largest possible conjugate, it would still be far to small to avoid renal clearance.

Accordingly, neither alone nor in combination do Copeland and Duncan yield the claimed conjugates.

The advantage of the much larger conjugate of applicant is demonstrated by the examples. The results shown in Example 12 (discussed below) are unexpected in view of the teachings of Duncan which requires the co-administration of an enzyme conjugate in order for the drug conjugate to be effective.

Example 12 describes the *in vivo* evaluation of the anti-tumor efficacy of dextran-oligopeptide-methotrexate conjugates. Six week old female SCID mice were injected with HT-1080 tumor cells. Free methotrexate, dextran-oligopeptide-methotrexate, or dextran-methotrexate was injected intraperitoneally on day 1, 8, and 15 after a tumor was first established. Weight and tumor size were monitored three times a week. The average tumor size was suppressed 92% by the dextran-oligopeptide-methotrexate and dextran-methotrexate compared to untreated animals (PBS), which was 44% more than the suppression seen with free methothrexate. **Linking methotrexate to a polymeric carrier, such as dextran, increases the half-life of the drug by decreasing renal elimination rendering the benefit of passive**

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targeting. Further in combination with an enzyme cleavage site containing a recognition segment yielding cleavage of the conjugate in the extracellular space of the tumor tissue where the enzyme is overexpressed results in greater delivery of therapeutic with decreased side effects.

The Examiner's attention is drawn to the specification at least at page 59, which discloses that dextran-methotrexate, albeit showing promising efficacy, was significantly more toxic than dextran-oligopeptide-methotrexate. Thus, not only do the claims provide a drug conjugate and a method of administering the drug conjugate that eliminates the need for an additional conjugate containing an enzyme as required by Duncan, this method of treatment is associated with decreased toxicity. This demonstrates both unexpected results and a solution to the long standing need for decreased systemic toxicity of chemotherapeutics - which is extremely important not just for the comfort of the patient but because the side effects are what usually limits the dosage used for treatment - and can prevent a patient from receiving an effective amount of drug.

U.S.S.N. 10/668,045

Filed: September 22, 2003

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Allowance of claims 1, 3, 5, 6, and 11-53, as amended, is respectfully solicited.

Respectfully submitted,

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Date: April 6, 2009

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